Serial Number: 09/549,858
Group Art Unit: 1614
Examiner: Jones, D.

REMARKS

Claims 1 to 23 are pending.

I. Rejection under 35 U.S.C. § 103(a) as Unpatentable over Oishi *et al.*, Japanese Patent Application H5-194225 ("JP '225")

Claims 1-23 are rejected under 35 U.S.C. § 103(a) as unpatentable over H5-194225 ("JP '225") ("Oishi *et al.*"). Applicants respectfully traverse this rejection.

The Examiner states that "Oishi *et al.* teach stabilized anti-ulcerative preparations, which contain an amino acid, namely glycine, and a benzimidazole compound, (see claims 1, 2 and 4)....The claims differ from the reference by reciting a more limited genus than the reference." Applicants respectfully disagree with the Examiner's characterization of Oishi *et al.*

Claims 1, 2 and 4 of the JP '225 Application are directed to "a preparation containing stabilized anti-ulcer agent, where amino acid, amino acid salt or amino acid alkali salt and buffer are blended as stabilization agents with benzimidazole compounds..." Further, Table I of JP '225 goes on to disclose that *the amino acid alone provides no stabilization* to the benzimidazole in solution (see entry "Control/Amino acid/Glycine 100 mg/External appearance after one day at 25°C/purple"). Finally, in section (0016) of the JP '225 Application, the applicants concede that "[t]he use of buffering agent alone or *the use of amino acid, amino acid salt or amino acid alkali salt alone provides absolutely no stabilization* effect when the substance is blended with benzimidazole compounds." Applicants respectfully submit that JP '225 does not anticipate the instant invention since the applicants in JP '225 clearly and unequivocally declare that "the amino acid alone or as an alkali salt provides no stabilization for benzimidazoles."

Additionally, the Examiner states that "it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the benzimidazole genus as taught by Oishi *et al.*, including those of the claims, because an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties..." Applicants respectfully disagree with the Examiner's conclusion. The

properties referred to by the Examiner must therefore also encompass the reported failed property of the amino acid alone, or the amino acid alkali salt alone, to stabilize the benzimidazoles, as reported by JP '225.

Therefore, Applicants assert that the JP '255 in fact teaches away from the claimed invention as it teaches that the use of amino acid, amino acid salt, or amino acid alkali salt alone provides no stabilization effect when blended with benzimidazole compounds.

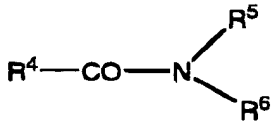
II. Rejection under 35 U.S.C. § 103(a) as Unpatentable over U.S. 5,536,735

Claims 1-23 are rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. 5,536,735 (" '735" patent) ("Takechi *et al.*"). Applicants respectfully traverse this rejection.

The Examiner asserts that "Takechi *et al.* teach a stable injectable preparation, which has anti-ulcerative activity and that contains an amino acid, namely glycine, and a benzimidazole compound, (see columns 1, 2, 5, 6 and column 8)." Applicants respectfully disagree.

Takechi *et al.* state in the '735 patent that, "the benzimidazole compound having antiulcer activity is highly soluble in an aqueous solution of *an amide, such as nicotinamide or benzamide*, and remains quite stable in such solution and that a composition obtainable by dissolving the compound in such an aqueous amide solution and lyophilizing or spray-drying the solution shows no coloration with time and offers a long shelf-life as well as good water-reconstitutability" (column 1, lines 52-59). Takechi goes on to state at column 1, lines 64-67, "[a]ccording to this invention, there is provided: 1) [a] pharmaceutical composition which comprises a benzimidazole compound having antiulcer activity and a water-soluble carboxylic acid *amide*..." Clearly, the '735 patent is teaching the stabilization of benzimidazoles using an amide. No mention is made of using glycine, or even an amino acid, as a stabilizer.

Takechi *et al.* further describe the compound responsible for the stability of the benzimidazole: "...the water-soluble carboxylic acid amide is a compound represented by the formula (II):



wherein R^4 is hydrogen, amino, an alkyl group which may optionally be substituted, an aryl group which may optionally be substituted or a N-containing heterocyclic group which may optionally be substituted, R^5 and R^6 are, the same or different, hydrogen or an alkyl group" (column 7, lines 15-28). This compound does not describe nor encompass glycine.

Additionally, at column 7, lines 51 to 55, Takechi gives specific examples of amides used: "[a]s specific examples of the water-soluble carboxylic amide can be mentioned nicotinamide, dimethylacetamide, dimethylformamide, benzoylamide, urea and so on. Nicotinamide is preferable."

Further, the specification does not describe the use of amino acids to stabilize the benzimidazole compounds of the '735 patent. Rather, the first mention of the use of amino acid is at column 6, line 57 to column 7, line 8:

> The benzimidazole compound or its salt for use in this invention can be produced by, inter alia, the processes described in the published literature such as Japanese and European laid-open patents and U.S. patents as mentioned hereinbefore, for example, U.S. Pat. No. 4,255,431, U.S. Pat. No. 4,508,905, U.S. Pat. No. 4,628,098, U.S. Pat. No. 4,738,975 and U.S. Pat. No. 5,312,824, or any processes analogous therewith.
>
> The salt of the benzimidazole compound is preferably a physiologically harmless salt. The physiologically harmless salt includes salts with inorganic bases, salts with organic bases, and salts with basic amino acids. Among the inorganic bases mentioned above are alkali metals (e.g. sodium, potassium, etc.) and alkaline earth metals (e.g. calcium, magnesium, etc.). The organic bases may be trimethylamine, triethylamine, pyridine, picoline, N,N-dibenzylethylenediamine, ethanolamine, diethanolamine, trishydroxymethylaminomethane, dicyclohexylamine, etc. The basic amino acids may be arginine, lysine and so on.

No mention is made here of stabilizing the benzimidazole compound using an amino acid, rather the topic addressed is "the production of the benzimidazole or benzimidazole salt for use in this invention."

The '735 patent goes on to describe the lyophilzation of benzimidazoles at column 8, lines 37 to 48:

> Where lyophilization is carried out, a form regulator may be added to an aqueous solution of the benzimidazole compound having antiulcer activity for the purpose of improving the morphology of the lyophilizate. The form regulator mentioned above includes various sugars (*e.g.* sugar alcohols such as mannitol, xylitol, inositol, sorbitol, etc., hexose-based disaccharides such as maltose, sucrose, lactose, etc., and monosaccharides such as glucose), neutral amino acids (*e.g.* glycine, alanine, proline, valine, methionine, etc.) and alkali metal salts of succinic acid (*e.g.* sodium succinate, etc.). Preferred, among these form regulators, are sugars. Particularly, sugar alcohols are preferred.

Here, a widely varying list of "form regulators" is given. Clearly stated is that the preferred "form regulator" for the lyophilzation of the benzimidazole "are ***sugars***. Particularly, sugar alcohols are preferred." Further, this is the first mention of glycine within the specification and it is amongst a long list of at least 14 possible "form regulators" and glycine is not listed as a "preferred" one.

Further, it is noteworthy that within the 10 claims of the '735 patent, glycine is not claimed in the stabilization of the benzimidazole. Rather, amides in general, and more particularly, nicotinamide, are claimed in the compositions stabilizing the benzimidazole. Therefore Takechi *et al.*, does not teach nor claim the stabilization of benzimidazoles through the use of glycine. Instead, this reference teaches stabilization through the use of amides.

Accordingly, Applicants submit that the instant claimed invention is not taught by Takechi *et al.* Applicants therefore request that the Examiner reconsider and withdraw this rejection.

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III. Conclusion

Applicants respectfully submit that all the bases for rejection of the pending claims are now moot. The Examiner is requested to reconsider the rejections and to withdraw them and to pass this case to issuance.

Respectfully submitted,

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